Medical Progress

Refer to: Deedwania PC: Calcium channel blockers (Medical Progress). West J Med 1982 Jul; 137:24-31

Calcium Channel Blockers

PRAKASH C. DEEDWANIA, MD, *Fresno, California*

Calcium (Ca^{++}) plays an essential role in many cardiovascular physiologic processes. Electrophysiologic properties of the sinus and atrioventricular nodes greatly depend on Ca^{++} ion influx. Also, Ca^{++} is the main link for excitation-contraction coupling of the myocardium. Ca^{++} channel blockers are a group of heterogeneous compounds that block the ionic influx of Ca^{++} into the myocardial and vascular smooth muscle cells. Because Ca^{++} plays a central role, it is not surprising that Ca^{++} channel blockers can produce profound alterations in cardiovascular functions. Recently several studies have shown these agents to be useful in the treatment of supraventricular tachyarrhythmia, variant angina, chronic stable angina and hypertrophic cardiomyopathy. In the future they may be found useful in preserving myocardium during cardiopulmonary bypass, in limiting infarct size and in the treatment of hypertension and congestive heart failure.

RECENTLY two calcium (Ca^{++}) channel blockers have been approved in the United States for the treatment of variant and chronic stable angina. Introduction of Ca^{++} channel blockers represents a considerable advancement in cardiovascular therapeutics and is indeed a welcome addition to the list of drugs available for the treatment of various cardiovascular disorders. The initial application of Ca^{++} channel blockers in the treatment of angina and supraventricular tachyarrhythmia represents only a few of the many indications (see Table 1) for which these agents are currently being investigated and have been found useful. In this article the role of Ca^{++} in cardiovascular physiology will be discussed and the basic pharmacology of Ca^{++} channel blockers as well as their clinical applications will be reviewed.

From the Departments of Cardiology and Internal Medicine, Veterans Administration Medical Center and University of California, San Francisco, Fresno Medical Education Program, Fresno.

Reprint requests to: Prakash C. Deedwania, MD, Chief, Cardiology Section, Veterans Administration Medical Center, 2615 E. Clinton Ave., Fresno, CA 93703.

Role of Ca^{++} in Cardiovascular Physiology

Ca^{++} ions play vital roles and are critical to the function of cardiac tissue and vascular smooth muscle. Ionic Ca^{++} has a key part in cardiac electrophysiologic processes, excitation-contraction coupling in myocardium and vascular smooth muscle and in control of energy storage and use.[1-3] Some of these important roles of Ca^{++} ions in various physiologic processes in the heart are illustrated in Figure 1.

Initially, on stimulation with a threshold stimulus, fast sodium (Na^{+}) channels open up at the cellular level and Na^{+} ions rush into the cell causing rapid depolarization (phase 0) (see Figure 2). This initial depolarization of the cell caused by inward movement of Na^{+} ions opens up the slow channels for Ca^{++} entry, allowing Ca^{++} ions to move inward during the plateau phase (phase 2) of the action potential.[3] Ca^{++}-carrying channels are called "slow channels" because they are several magnitudes slower than the "fast chan-

ABBREVIATIONS USED IN TEXT

AV = atrioventricular
Ca^{++} = calcium
cyclic AMP = adenosine 3′:5′-cyclic phosphate
FDA = Food and Drug Administration
Na^{+} = sodium
PSVT = paroxysmal supraventricular tachycardia
SA = sinoatrial

TABLE 1.—*Potential Clinical Applications of Calcium Channel Blockers*

Cardiac arrhythmia
Vasospastic angina
Chronic stable angina
Hypertrophic cardiomyopathy
Systemic hypertension
Congestive heart failure
Pulmonary hypertension
Myocardial preservation

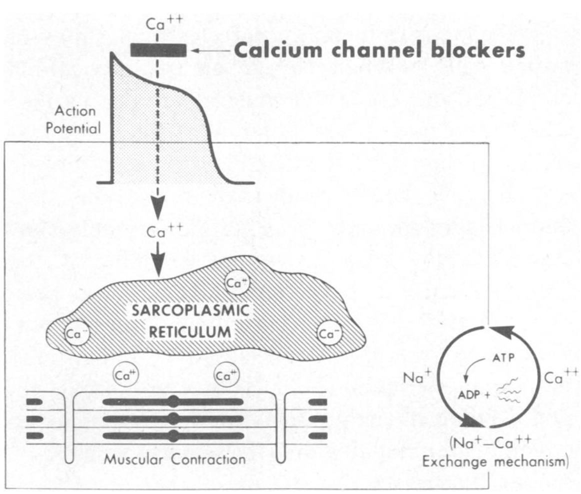

Figure 1.—Role of calcium in myocardial excitation-contraction coupling. Ca^{++} channel blockers act at the first step by blocking the influx of Ca^{++} ions during plateau phase of cardiac action potential. Ca^{++} = calcium, Na^{+} = sodium, ATP = adenosine triphosphate, ADP = adenosine diphosphate.

nels" of Na^{+}.[4,5] Slow channels depend on two kinds of stimuli—one is voltage-dependent and the other depends on activation of a protein kinase by adenosine 3′:5′-cyclic phosphate (cyclic AMP).[2,5] The Ca^{++} ions entering the cell during the plateau phase trigger release of larger quantities of Ca^{++} ions from sarcoplasmic storage sites. Once the intracellular concentration of Ca^{++} reaches above 10^{-7} M, it removes the inhibitory influence of the troponin-tropomyosin complex on the interaction between actin and myosin, and contraction ensues (see Figure 1). Thus the Ca^{++} entry into the cell

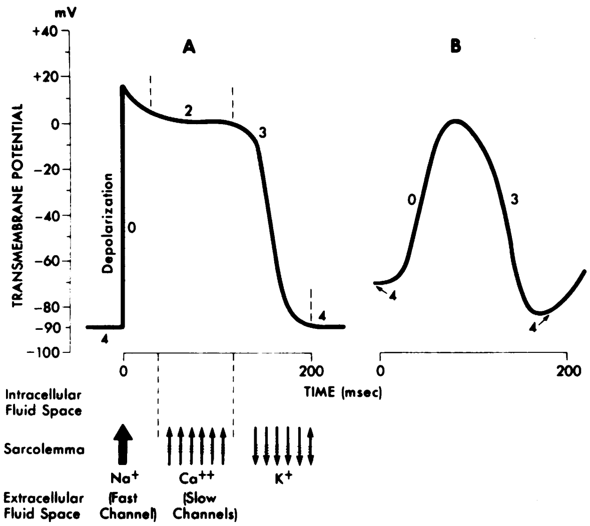

Figure 2.—Fast **(A)** and slow **(B)** cardiac action potentials in the heart. Calcium enters the cell during the phase 2 (plateau) of fast action potential **(A)** and slow action potential **(B)** depends mostly on Ca^{++} ions for its activation. msec = milliseconds, mV = millivolts, Na^{+} = sodium, Ca^{++} = calcium, K^{+} = potassium.

has an essential function in the excitation-contraction coupling in the myocardium.[1,6] Similarly, the extent of contraction of smooth muscle in the systemic and coronary vascular beds is dependent on the entry of Ca^{++} ions into the vascular smooth muscle cells.[1,6]

Ca^{++} Channel Blockers

Initially Ca^{++} channel blockers prenylamine and verapamil were introduced in Germany as coronary vasodilators for the treatment of angina pectoris.[7,8] Because these agents were found to produce inotropic and chronotropic effects that were opposite to those elicited by catecholamines, they were initially thought to be adrenergic blocking agents.[9,10] It was not until 1967 that pioneering studies of Fleckenstein and co-workers[11] showed that the action of these agents differed from those of beta blockers and was related to inhibition of the influx of Ca^{++} ions into myocardial cells. Consequently, the agents were named "Ca^{++} antagonists."[5] Later, in 1970 Fleckenstein[12] specified that Ca^{++} antagonists act by reversibly sealing specific Ca^{++} channels in the membrane of the mammalian myocardial cell.

These agents have been known variously as Ca^{++} antagonists, Ca^{++} channel blockers, Ca^{++} entry blockers, slow channel inhibitors and Ca^{++} inhibitors. But because they are known to antagonize Ca^{++} only at specific sites in the sarcolemma (the slow channel) and do not have a significant effect

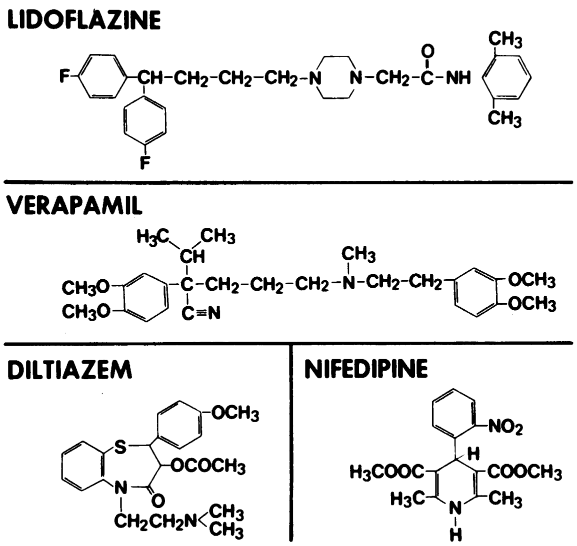

Figure 3.—Chemical structure of four different calcium channel blocking agents. Note the dissimilarity in their structure.

TABLE 2.—*General Properties of Calcium (CA^{++}) Channel Blockers*

May decrease cardiac pacemaker (SA nodal) activity
Usually increase AV nodal refractoriness
Cause myocardial excitation-contraction uncoupling (negative inotropic effect)
Reduce coronary vascular resistance (increase coronary flow)
Reduce systemic vascular resistance (decrease blood pressure)
Actions reversed by Ca^{++} or catecholamines

SA = sinoatrial, AV = atrioventricular

on a wide variety of Ca^{++} binding and transport systems, it is more accurate to refer to them as Ca^{++} channel blockers or slow channel inhibitors.[13]

Over the last two decades many new Ca^{++} channel blockers have been developed and introduced and now the list includes diltiazem, flunarizine, lidoflazine, nifedipine, niludipine, perhexiline, prenylamine, verapamil and D_{600} (the methoxy derivative of verapamil). However, most of the clinical studies in progress are evaluating nifedipine, diltiazem, verapamil and lidoflazine in the treatment of various cardiovascular disorders.

Pharmacology of Ca^{++} Channel Blockers

Ca^{++} channel blockers are a group of heterogeneous compounds. Although Ca^{++} channel blockers in general inhibit slow channel activity, unlike β-blockers these agents vary considerably in their chemical structure (see Figure 3) and overall actions in the cardiovascular system.[14,15] These differences are clinically important and may be related to quantitative differences in their ability to inhibit excitation-contraction coupling in cardiac tissue or vascular smooth muscle, effects on sinoatrial (SA) nodal automaticity or atrioventricular (AV) nodal conduction properties. Such variations would undoubtedly account for the difference in their net electrophysiologic effects, hemodynamic effects, overall therapeutic implications and adverse reactions. Table 2 shows some important general properties of Ca^{++} channel blockers.

Electrophysiologic Effects

Sinus and AV nodal cells have slowly rising action potential and are predominantly depolarized by inward movement of Ca^{++} ions (see **B** of Figure 2). Because of their dependence on Ca^{++} ions, automaticity of the SA and AV nodes and their velocity of conduction are greatly influenced by Ca^{++} channel blockers. Ca^{++} ions may also play a significant role in abnormal electrical states of cardiac cells.[16] When Na^{+}-dependent myocardial cells (atrial or ventricular muscle) are depolarized due to increased extracellular potassium (for example, in myocardial ischemia) or stretch, the Na^{+} channels become inactivated and the slow channels predominate.[16,17] These abnormally slow responses may play an important role in the genesis of cardiac arrhythmia.[18] It has also been proposed that triggered automaticity may occasionally be responsible for supraventricular and ventricular arrhythmias.[18] These abnormal response-induced arrhythmias and those due to triggered automaticity may be abolished by Ca^{++} channel blockers.[18,19]

Most studies of the cardiac electrophysiologic effects of Ca^{++} channel blockers have been conducted with verapamil.[20] In isolated preparation separated from extrinsic neural influences, verapamil decreases the spontaneous firing rate of the SA node.[20] This effect on the SA node is in part due to its direct inhibitory action on the Ca^{++} current and in part related to its noncompetitive antisympathetic actions.[21] However, in intact circulation these changes are greatly modified due to the drug's peripheral vasodilatory properties. The resulting hypotension causes reflex tachycardia, thereby neutralizing any direct negative chronotropic effects. In the AV node, verapamil and other Ca^{++} channel blockers (except nifedipine) slow AV nodal conduction and increase the duration of refractoriness without affecting the resting potential.[20-23] It is this property of Ca^{++}

TABLE 3.—*Electrophysiologic Effects of Ca^{++} Channel Blockers*

May suppress sinoatrial pacemaker activity
Prolong sinus node recovery time
No significant effect on intra-atrial conduction
Significant increase in AH interval (increased AV nodal delay)
Increase ERP and FRP of AV node
No significant effect on His ventricle interval
No effect on intraventricular conduction time
Variable effects on accessory pathway conduction (may shorten Kent's bundle ERP)

AH=atrio-His, AV=atrioventricular, ERP=effective refractory period, FRP=functional refractory period

channel blockers that makes them so useful in the treatment of supraventricular arrhythmia, especially AV nodal reentrant tachycardia.[20-24] In addition, verapamil has been found to decrease triggered automaticity or abolish abnormal depolarization in Purkinje's fibers.[18] Verapamil may shorten the effective refractory period of the accessory pathway in patients with the Wolff-Parkinson-White syndrome and thus may be harmful in such patients.[25] Ca^{++} channel blockers have no significant effect on infranodal conduction times or on intra-atrial or ventricular conduction times. The electrophysiologic effects of Ca^{++} channel blockers are summarized in Table 3.

Hemodynamic Effects

Hemodynamic effects of Ca^{++} channel blockers are the net result of a complex interplay of simultaneous changes in heart rate, cardiac contractility, systemic vascular resistance and coronary blood flow.[26] Vascular smooth muscle tone in systemic and coronary arteries is greatly dependent on the intracellular concentration of Ca^{++} ions.[1,2] Ca^{++} channel blockers inhibit the influx of Ca^{++} ions and thus cause vasodilation and significant reduction in coronary and systemic vascular resistance.[26] Ca^{++} channel blockers have been found to counteract the coronary vasoconstriction induced by norepinephrine, angiotensin, methacholine, potassium (K^+) or barium chloride.[27] Ca^{++} channel blockers increase blood flow not only in coronary, but also in mesenteric and renal circulation. The systemic vasodilatory effects have been found to cause reduction in blood pressure and to increase reflexively myocardial contractility.[26] Ca^{++} channel blockers by their negative effect on excitation-contraction coupling directly decrease myocardial contractility.[6,26] However, this effect is mostly counterbalanced by the reflexive increase in contractility due to peripheral vasodilation caused by these agents.[28]

Although it is not possible here to describe various properties of individual Ca^{++} channel blockers, some general considerations and discussion of important differences is warranted. It must be reemphasized that though the common property of all Ca^{++} channel blockers is to block the entry of Ca^{++} ions into the cell, there could be considerable differences between their pharmacologic properties. Such differences in the pharmacologic properties of verapamil and nifedipine clearly account for the variability of their clinical application. Nifedipine depresses slow channel activity in the myocardium but has minimal depressant effect on the SA node or AV nodal conduction.[14] Such differences in the action of nifedipine as compared with those of verapamil may be due to the fact that nifedipine reduces the number of channels but does not alter the time course of the activation, inactivation or recovery from inactivation of the slow channel.[15] Verapamil, in contrast, has a marked influence on all these properties of the slow channels and in addition has some muscarinic blocking activity.[20] Because of the relative lack of electrophysiologic effects, nifedipine, unlike verapamil, is not useful in the treatment of supraventricular tachyarrhythmia. Verapamil, on the other hand, has less vasodilatory effect and may even have an adverse effect on myocardial contractility, especially in patients with preexisting left ventricular dysfunction.[28]

Clinical Applications

Because Ca^{++} plays a central role in many cardiovascular physiologic processes, it is not surprising that Ca^{++} channel blockers possess many important clinical properties (see Table 2). These actions can be useful in the treatment of a wide variety of clinical disorders that include (1) various cardiac arrhythmias, especially AV nodal reentrant tachycardia and atrial flutter and fibrillation; (2) myocardial ischemic syndromes, including Prinzmetal's angina (coronary artery spasm), chronic stable angina and possibly unstable angina; (3) hypertrophic cardiomyopathy, and (4) arterial hypertension. Although not firmly established, these agents have also been found useful in the treatment of congestive heart failure, in limiting myocardial infarct size and in myocardial preservation during cardiopulmonary bypass. The Food and Drug Administration (FDA) has approved verapamil in its intravenous form for treatment of supraventricular tachyarrhythmia. Recently orally given verapamil and nifedipine have also been approved for use in Prinzmetal's and chronic stable angina. Diltiazem is still being evaluated by the FDA for approval as an antianginal agent.

In Cardiac Arrhythmia

Verapamil is by far the most widely studied Ca^{++} channel blocker in the treatment of cardiac arrhythmia.[20] It is considered the drug of choice for the treatment of paroxysmal supraventricular tachycardia (PSVT).[20-24] Several earlier studies have indicated that more than 80 percent of cases of PSVT can be promptly relieved by verapamil with very few side effects.[20-24] In a recent double-blind randomized crossover study, Waxman and associates[29] reported a 79 percent conversion rate in patients with PSVT and a 65 percent success rate in slowing the ventricular response in patients with atrial fibrillation or flutter.

In patients with AV nodal reentrant tachycardia, 5 to 10 mg of verapamil given intravenously terminates the tachycardia within two to five minutes of administration.[23] The mode of termination of PSVT by verapamil is not uniform, for it may occur as (1) abrupt termination, (2) initial slowing with eventual conversion to sinus rhythm, (3) transient atrial filbrillation followed by conversion to a normal sinus rhythm (NSR), (4) occurrence of premature ventricular contraction before conversion or (5) alteration in cycle length of the tachycardia before conversion.[20] Verapamil should be used with caution in patients with Wolff-Parkinson-White syndrome and atrial fibrillation because it can shorten the effective refractory period of the Kent's bundle, thus increasing the number of fibrillatory impulses that can traverse down the accessory pathway, possibly inducing ventricular fibrillation.[25] However, verapamil is considered to be an effective agent in the treatment of sustained supraventricular tachycardia in patients with overt and concealed Wolff-Parkinson-White syndrome; by slowing conduction at the AV node it breaks the reentrant circuit.[20] In patients with atrial flutter or fibrillation, verapamil has been found to effectively slow the ventricular response rate.

In a recent study[29] verapamil, when given as a bolus injection, was significantly more effective than placebo in slowing the ventricular rate in patients with atrial fibrillation. Klein and colleagues[30] recently evaluated the effects of verapamil in patients with chronic atrial fibrillation who were already receiving therapeutic dosages of digitalis. Verapamil substantially reduced the exercise-induced increase in the ventricular response rate in these patients.

Ca^{++} channel blockers are not very useful in the treatment of ventricular arrhythmia.[20-23] Some recent animal studies have shown these agents to be useful in controlling the arrhythmia produced by acute coronary occlusion.[31] Further studies are needed to establish their usefulness in arrhythmia produced as a result of myocardial ischemia.

In Anginal Syndromes

Angina is caused by an imbalance between myocardial oxygen demand and supply. Exertional angina usually occurs due to an excessive increase in myocardial oxygen demand in the presence of limited coronary artery blood flow. Angina at rest, however, has been shown in most cases to be due not to an increase in myocardial oxygen demand but rather to a primary reduction in oxygen delivery. Also, there is increasing evidence that whereas exertional angina is usually associated with fixed coronary artery obstructive lesions, angina at rest has been found often to occur as a result of coronary artery spasm and transient platelet aggregates.[32,33] Over the past several years there have been increasing belief in and evidence to suggest that coronary artery spasm plays a significant role in all varieties of myocardial ischemic syndromes.

At present the medical management of anginal syndromes is limited to the administration of β-blockers and nitrates. Patients may not fully respond to these agents, however, and occasionally intolerance develops due to side effects. In addition, β-blockers must be administered with caution in patients with bronchospastic pulmonary diseases or diabetes mellitus. Many recent studies have shown that Ca^{++} channel blockers are quite effective in the treatment of patients with coronary artery spasm and chronic stable angina.[34-50]

Ca^{++} channel blockers are unique agents for the treatment of anginal syndromes. Figure 4 shows that they possess hemodynamic properties comparable with those seen with nitrates and β-blocker combination therapy. Like β-blockers, these agents decrease myocardial oxygen demand by their negative inotropic and chronotropic effects. These effects are most apparent during exercise. In addition, Ca^{++} channel blockers are

COMPARATIVE ANTIANGINAL PROPERTIES OF VARIOUS AGENTS

Hemodynamic Parameter	Nitrates	β-Blockers	CA + + Channel Blockers
Heart rate	↑←	↓↓	↓
Blood pressure	↓	↓↓↓	↓↓
Myocardial contractility	→	↓	↓↑
Preload	↓↓	↑→	↑→
Afterload	↓	↑←	↓↓
Myocardial wall tension	↓	↑	
Myocardial O2 requirement	↓	↓	↓
Coronary vascular resist.	↓↓	↑	↓↓
Coronary blood flow (O2 supply)	↑←	↓	↑
Subepi./subendo. blood flow	→↑	—	↑↑
Mitochondrial preservation	—	—	+

Figure 4.—Various important hemodynamic parameters governing myocardial oxygen demand and supply are shown and actions of conventional antianginal agents—nitrates and β-blockers—are compared with those of Ca^{++} channel blockers. Ca^{++} = calcium, O_2 = oxygen, resist = resistance, subepi = subepicardial, subendo = subendocardial, ↑ = increase, ↓ = decrease, → = no change, ← = no change, — = no information available, + = present.

potent coronary and systemic vasodilators, thus relieving coronary artery spasm, increasing coronary artery blood flow and decreasing the workload for the myocardium by reducing the afterload.

In Coronary Artery Spasm

Because Ca^{++} channel blockers are potent coronary vasodilators, there has been considerable interest in using them for treating patients with variant angina. Several studies have evaluated nifedipine, diltiazem, verapamil and perhexiline for the treatment of coronary artery spasm.[34-41] In a recently published multicenter study Antman and co-workers[34] summarized that in patients with coronary artery spasm, most of whom had previously been treated unsuccessfully with conventional antianginal medication, nifedipine eliminated the spontaneous attack and ST segment elevation in 63 percent of the patients, and in 87 percent of the patients the frequency of anginal attacks decreased by at least 50 percent. Rosenthal and associates[38] have found diltiazem to be quite effective also for the control of symptoms related to active coronary artery spasm. Similarly, verapamil has been effective in the treatment of exercise-induced coronary artery spasm.[39] A recent multi-institutional study in Japan evaluated the comparative clinical efficacy of nifedipine, diltiazem and verapamil in 286 patients with variant angina. Nifedipine, diltiazem and verapamil were effective in 94.0 percent, 90.8 percent and 85.7 percent, respectively.[40] In yet another study Waters and colleagues[41] provided objective evidence of efficacy by showing that nifedipine, diltiazem and verapamil can partially or completely block ergonovine-induced angina and ST segment elevation in most patients with variant angina. Thus there is little doubt that Ca^{++} channel blockers are quite effective in the treatment of patients with variant angina.

In Chronic Stable Angina

Currently available antianginal agents, β-blockers and nitrates, are ineffective or cause intolerable side effects in a substantial number of patients. Ca^{++} channel blockers seem to overcome some of these problems and appear to be promising therapeutic adjuncts for treating patients with stable angina.

The antianginal properties of Ca^{++} channel blockers have been discussed above. In summary, these agents are vasodilators and negative inotropic and chronotropic agents; thus they not only reduce myocardial oxygen demand, but may also increase the delivery of blood to ischemic areas. Various Ca^{++} channel blockers have been shown to control the exercise-induced increments in rate-pressure product and thus provide relief for exercise-induced angina. Finally, inappropriate vasoconstriction may play a part in causing chronic stable angina and Ca^{++} channel blockers, because of their coronary vasodilatory properties, are also effective in relieving such vasoconstriction.

Several recent studies have evaluated the clinical efficacy of Ca^{++} channel blockers in the treatment of stable angina patients. Worldwide experience using nifedipine in more than 4,000 patients for periods ranging from two weeks to three years showed beneficial results in patients with angina pectoris.[42] In a recently published multicenter double-blind, placebo-controlled study, Mueller and Chahine[43] summarized that nifedipine decreased the frequency of anginal attacks and the intake of nitroglycerin by about 50 percent; exercise tolerance was also noted to have increased significantly in the treated group. Similarly, verapamil, as compared with a placebo, has been found to decrease the frequency of angina and prolong exercise duration.[44] Hossack and Bruce[45] have recently reported that high dosages of diltiazem (240 mg a day) substantially increased the duration of exercise and the time to the first onset of angina in patients with chronic stable angina.

Several studies have compared the efficacy of

Ca^{++} channel blockers with other conventional antianginal agents. Kaltenbach[46] has shown that nifedipine, propranolol, pindolol and nitroglycerin used in comparable dosages were equally effective in controlling the degree of ST segment depression during exercise tolerance testing. Kimura and co-workers[47] have shown nifedipine to be as effective as isosorbide dinitrate in treatment of patients with angina pectoris. In a recent study Johnson and associates[48] compared the relative efficacy of propranolol and verapamil in patients with stable angina pectoris. Verapamil was found to be equally or more efficacious in alleviating symptoms of angina pectoris and the need for nitroglycerin. A recent report by Leon and colleagues[49] showed that the combination of verapamil and propranolol produced a greater antianginal effect than that achieved by either drug alone and may be considered suitable treatment for patients with severe angina refractory to single-drug therapy. Further studies are needed to establish the safety of such a combination because both propranolol and verapamil have a depressant effect on SA and AV nodes.

Ca^{++} channel blockers may be useful in patients with angina refractory to conventional antianginal therapy. In a recent study Moses and co-workers[50] have found nifedipine to be efficacious in the treatment of rest angina patients with obstructive coronary artery disease who were previously refractory to propranolol and nitrate therapy. Although further studies are needed to determine long-term efficacy and adverse effects of Ca^{++} channel blockers in the treatment of angina pectoris, there is no doubt that these agents will prove to be important adjuncts to currently available regimens.

In Hypertrophic Cardiomyopathy

Administration of β-blocking drugs is now considered to be the treatment of choice for patients with hypertrophic cardiomyopathy. Occasionally such treatment is inadequate in controlling symptoms and a patient usually needs to be referred for surgical intervention. Ca^{++} channel blockers now provide an effective alternative in such refractory patients. Rosing and associates[51] have shown verapamil to be extremely effective in controlling symptoms of patients with hypertrophic cardiomyopathy and long-term studies[52,53] have shown that treatment with verapamil improves their exercise capacity considerably. Although the exact mechanism of its beneficial action in patients with hypertrophic cardiomyopathy is not known, it may be due to the drug's negative inotropic effect, combined with its ability to increase the rate of ventricular filling.[52,54]

Potential Applications

Although not well established, Ca^{++} channel blockers have been found useful in systemic hypertension,[55] pulmonary hypertension,[56] and congestive heart failure.[57] Experimental studies[58-60] during acute coronary occlusion have shown Ca^{++} channel blockers to have a myocardial protective effect and that they limit the degree of ischemic damage in experimental animals. These data need to be established further and clinical studies be done before any conclusions can be drawn regarding the clinical usefulness of these agents in acute myocardial infarction.

Summary

The development of Ca^{++} channel blockers indeed represents an important milestone in cardiovascular treatment. Verapamil in its intravenous form is now available for use in the treatment of supraventricular tachyarrhythmias. Oral preparations of verapamil and nifedipine have recently been approved by the FDA for treatment of variant angina and chronic stable angina refractory to conventional therapy. Several Ca^{++} channel blockers are being evaluated for treatment of patients with unstable angina, acute myocardial infarction and other ischemic syndromes. In the future, these agents may also prove to be of clinical use in hypertension, congestive heart failure and in myocardial preservation.

REFERENCES

1. Fleckenstein A: Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. Annu Rev Pharmacol Toxicol 1977; 17:149-166
2. Ratz PH, Flaim SF, Zelis R: Excitation-contraction coupling in bovine coronary artery—Predominance of potential dependent calcium channels. Circulation 1980; 62(Suppl III):253-255
3. Carmeliet E, Vereecke J: Adrenaline and the plateau phase of the cardiac action potential—Importance of Ca^{++}, Na^{+} and K^{+} conductance. Pfluegers Arch 1969; 313:300-315
4. Kohlhardt M, Bauer B, Krause H, et al: Differentiation of the transmembrane Na^{+} and Ca^{++} channels in mammalian cardiac fibers by the use of specific inhibitors. Pfluegers Arch 1972; 335:309-322
5. Reuter H: Properties of two inward membrane currents in the heart. Annu Rev Physiol 1979; 41:413-424
6. Langer GA: Heart: Excitation-contraction coupling. Annu Rev Physiol 1973; 35:55-86
7. Lindner E: Phenyl-propyl-diphenyl-propyl-amin, eine neue Substanz mit koronargefässerweiternden Wirkung. Arzneimittelforsch 1960; 10:569-573
8. Haas H, Härtfelder G: α-Isopropyl-α-(N-methylhomoveratryl-γ-aminopropyl)-3, 4-dimethoxy-phenylacetonitrol, eine Substanz mit koronargefässerweiternden Eigenschaften. Arzneimittelforsch 1962; 12:549-558
9. Melville KL, Benfey BC: Coronary vasodilatory and cardiac adrenergic blocking effects of iproveratril. Can J Physiol Pharmacol 1965; 43:339-342
10. Haas H, Busch E: Vergleichende Untersuchungen der Wirkung von α-Isopropyl-α-(N-methyl-N-homoveratryl)γ-aminopropyl)-3,4-dimethoxy-phenylacetonitril, seiner Derivate sowie einiger

anderer Koronardilatatoren und β-receptor-affiner Substanzen. Arzneimittelforsch 1967; 17:257-272

11. Fleckenstein A, Kammermeier H, Döring HJ, et al: Zum Wirkungsmechanismus neuartiger Koronardilatatoren mit gleichzeitig Sauerstoff-einsparenden Myokard-Effekten, Prenylamin und Iproveratril. Z Kreislaufforsch 1967 Jul, Aug: 56:716-744, 839-858

12. Fleckenstein A: Die Zügelung des Myocardstoffwechsels durch Verapamil—Angriffspunkte und Anwendungsmöglichkeiten. Arzneimittelforsch 1970 Sep; 20:1317-1322

13. Katz A, Renter H: Cellular calcium and cardiac cell death. Am J Cardiol 1979 Jul; 44:188-190

14. Henry PD: Calcium ion (Ca^{++}) antagonists: Mechanism of action and clinical application. Prac Cardiol 1979; 5:145-156

15. Kohlhardt M, Fleckenstein A: Inhibition of the slow inward current by nifedipine in mammalian ventricular myocardium. Naunyn Schmiedebergs Arch Pharmacol 1977 Jul 18; 298(3): 267-272

16. Pappano AJ: Calcium-dependent action potentials produced by catecholamines in guinea pig atrial muscle fibers depolarized by potassium. Circ Res 1970; 27:379-390

17. Schneider JA, Sperlakis N: Slow Ca^{++} and Na^{+} responses induced by isoproterenol and methyxanthines in isolated perfused guinea pig hearts exposed to elevated K^{+}. J Mol Cell Cardiol 1975; 7:249-273

18. Zipes DP, Besch HR, Watanabe AM: Role of the slow current in cardiac electrophysiology. Circulation 1975 May; 51: 761-766

19. Singh BN, Collett JT, Chew CYC: New perspectives in the pharmacologic therapy of cardiac arrhythmias. Prog Cardiovasc Dis 1980 Jan-Feb; 22:243-301

20. Singh BN, Ellrodt G, Peter CT: Verapamil: A review of its pharmacological properties and therapeutic use. Drugs 1978 Mar; 15:169-197

21. Ellrodt G, Chew CYC, Singh BN: Therapeutic implications of slow channel blockade in cardiocirculatory disorders. Circulation 1980 Oct; 62:669-679

22. Wit AL, Cranefield PF: Effect of verapamil on the sinoatrial and atrioventricular nodes of the rabbit and the mechanism by which it arrests reentrant atrioventricular nodal tachycardia. Circ Res 1974 Sep; 35:413-425

23. Schmaroth L, Kirkler DM, Garrett C: Immediate effects of intravenous verapamil in cardiac arrhythmia. Br Med J 1972; 1: 660-664

24. Krikler DM, Spurrell RA: Verapamil in the treatment of paroxysmal supraventricular tachycardia. Postgrad Med 1974; 50:447-453

25. Spurrell RA, Krikler DM, Sowton E: Effects of verapamil on electrophysiological properties of anomalous atrioventricular connexion in Wolff-Parkinson-White syndrome. Br Heart J 1974 Mar; 36:256-264

26. Stone PH, Entman EM, Mueller JE, et al: Calcium channel blocking agents in the treatment of cardiovascular disorder—Part II: Hemodynamic effects and clinical applications. Ann Intern Med 1980 Dec; 93:886-904

27. Ginsburg R, Bristow MR, Harrison D, et al: Studies with isolated human coronary arteries—Some general observations, potential mediators of spasm, role of calcium antagonist. Chest 1980 Jul; 78(Suppl):180-186

28. Singh BN, Roche AHG: Effects of intravenous verapamil on hemodynamics in patients with heart disease. Am Heart J 1977; 94:593-599

29. Waxman HL, Myerburg RJ, Appel R, et al: Verapamil for control of ventricular rate in paroxysmal supraventricular tachycardia and atrial flutter-fibrillation—A double blind randomized crossover study. Ann Intern Med 1981 Jan; 94:1-6

30. Klein HO, Panzner H, Segin ED, et al: The beneficial effects of verapamil in chronic atrial fibrillation. Arch Intern Med 1979; 139:747-749

31. Fondacaro JD, Han J, Yoon MS: Effects of verapamil on ventricular rhythm during acute coronary occlusion. Am Heart J 1978 Jul; 96:81-86

32. Maseri A, Severi S, Nes MD, et al: 'Variant' angina: One aspect of a continuous spectrum of vasospastic myocardial ischemia—Pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. Am J Cardiol 1978 Dec; 42:1019-1035

33. Folts JD, Crowell EB Jr, Rowe GG: Platelet aggregation in partially obstructed vessels and its elimination with aspirin. Circulation 1976; 54:365-370

34. Antman E, Muller JE, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm—Experience in 127 patients. N Engl J Med 1980 Jun; 302(23):1269-1273

35. Heupler FA Jr, Proudfit WL: Nifedipine therapy for refractory coronary arterial spasm. Am J Cardiol 1979 Oct 22; 44(5): 798-803

36. Théroux P, Waters DD, Affaki GS, et al: Provocative testing with ergonovine to evaluate the efficacy of treatment with calcium antagonists in variant angina. Circulation 1979 Sep; (60): 504-510

37. Raabe DS Jr: Treatment of variant angina pectoris with perhexiline maleate. Chest 1979 Feb; 75:152-156

38. Rosenthal SJ, Ginsburg R, Lamb I, et al: Efficacy of diltiazem for control of symptoms of coronary arterial spasm. Am J Cardiol 1980 Dec; 46:1027-1032

39. Freedman B, Dunn RF, Richmond DR, et al: Coronary artery spasm during exercise: Treatment with verapamil. Circulation 1981; 64:68-75

40. Kimura E, Kishida H: Treatment of variant angina with drugs: A survey of 11 cardiology institutes in Japan. Circulation 1981; 63:844-848

41. Waters DD, Théroux P, Szlachcic-Brynczak J, et al: Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem and verapamil in variant angina. Am J Cardiol 1981; 48:123-129

42. Ebner F, Dunschede HB: Hemodynamics, therapeutic mechanisms of action and clinical findings of Adalat use based on worldwide clinical trials, *In* Jatene AD, Lichlen PR (Eds): The Third International Adalat Symposium. Amsterdam, Excerpta Medica, 1976, pp 283-300

43. Mueller HS, Chahine RA: Interim report of multicenter double blind, placebo-controlled studies of nifedipine in chronic stable angina. Am J Med 1981 Oct; 71:645-657

44. Livesley B, Catley PF, Campbell RC, et al: Double-blind evaluation of verapamil, propranolol, and isosorbide dinitrate against a placebo in the treatment of angina pectoris. Br Med J 1973 Feb 17; 1:375-378

45. Hossack KF, Bruce RA: Improved exercise performance in persons with stable angina pectoris receiving diltiazem. Am J Cardiol 1981 Jan; 47:95-101

46. Kaltenbach M: Assessment of antianginal substances by means of ST depression in the exercise EKG, *In* Hashimoto K, Kimura E, Kobayashi T (Eds): New Therapy of Ischemic Heart Disease. Proceedings of the First International Nifedipine "Adalat" Symposium, Tokyo, Nov 24-25, 1973. Tokyo, Tokyo University Press, 1975, pp 126-135

47. Kimura E, Mabuchi G, Kikuchi H: Clinical evaluation of the effect of nifedipine on angina pectoris by sequential analysis, *In* Hashimoto K, Kimura E, Kobayashi T (Eds): New Therapy of Ischemic Heart Disease. Proceedings of the First International Nifedipine "Adalat" Symposium, Tokyo, Nov 24-25, 1973. Tokyo, Tokyo University Press, 1975, pp 155-159

48. Johnson SM, Mauritson DR, Corbett JR, et al: Double blind, randomized placebo-controlled comparison of propranolol and verapamil in the treatment of patients with stable angina pectoris. Am J Med 1981 Sep; 71:443-451

49. Leon MB, Rosing DR, Bonow RO, et al: Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. Am J Cardiol 1981 Jul; 48:131-139

50. Moses JW, Wertheimer JH, Bodenheimer MM, et al: Efficacy of nifedipine in rest angina refractory to propranolol and nitrates in patients with obstructive coronary artery disease. Ann Intern Med 1981 Apr; 94:425-429

51. Rosing DR, Kent BM, Borer JS, et al: Verapamil therapy: A new approach to the pharmacologic treatment of hypertrophic cardiomyopathy—I. Hemodynamic effects. Circulation 1979 Dec; 60:1201-1207

52. Rosing DR, Kent KM, Maron BJ, et al: Verapamil therapy: A new approach to the pharmacologic treatment of hypertrophic cardiomyopathy—II. Effects on exercise capacity and symptomatic status. Circulation 1979 Dec; 60:1208-1213

53. Kaltenbach M, Hopf R, Kober G, et al: Treatment of hypertrophic cardiomyopathy with verapamil. Br Heart J 1979 Jul; 42:35-42

54. Raff GL, Brundage BH, Ports TA, et al: Disassociation between acute hemodynamic effects and clinical response to verapamil in hypertrophic cardiomyopathy. Clin Res 1981; 29:1,79A

55. Olivari MT, Bartorelli C, Polese A, et al: Treatment of hypertension with nifedipine, a calcium antagonistic agent. Circulation 1979 May; 59:1056-1062

56. Klugman S, Fioretti P, Camerini F: Acute hemodynamic effects of nifedipine in pulmonary hypertension. Circulation 1980 Oct; 62(II):503A

57. Matsumoto S, Ito T, Sada T, et al: Hemodynamic effects of nifedipine in congestive heart failure. Am J Cardiol 1980; 46: 476-480

58. Nagao T, Matlib MA, Franklin D, et al: Effects of diltiazem, a calcium antagonist, on regional myocardial function and mitochondria after brief coronary occlusion. J Mol Cell Cardiol 1980; 12:39-43

59. Nayler WG, Ferrari R, Williams A: Protective effect of pretreatment with verapamil, nifedipine and propranolol on mitochondrial function in the ischemic and reperfused myocardium. Am J Cardiol 1980 Aug; 46:242-248

60. Hattori S, Weintraub WW, Agarwal JB, et al: The effects of nifedipine on ischemic myocardium: Preservation of contraction during partial coronary occlusion, abstract. Am J Cardiol 1980; 45:484